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Gerger, Heike ; Hlavica, Michaela ; Gaab, Jens ; Munder, Thomas ; Barth, Jürgen

Abstract: Background: Patients with medically unexplained symptoms (MUS) are difficult to treat and cause high health-care costs. Psychological interventions might be a beneficial option for treating patients with MUS, but evidence is inconsistent. This meta-analysis compares the effectiveness of psychological interventions for MUS - delivered either by psychotherapists (PTs) or by general practitioners (GPs) - with that of usual care. Method: We conducted a systematic review and meta-analysis on randomised controlled trials of psychological interventions for MUS. Physical symptoms were the primary outcome, and physical functioning and psychological symptoms were the secondary outcomes. We pooled between-group effect sizes (ESs) after the treatment and at the follow-up in random-effects meta-regressions and stratified meta-analyses. We repeated these analyses with the intervention provider, intervention dose, MUS severity and methodological quality as predictors of relative intervention effects. Results: A total of 3,225 patients in 20 studies were analysed. After the treatment, small and significant ESs were found for all 3 outcome domains (ES range: 0.13-0.19, all $p < 0.05$). Psychological interventions were more beneficial for physical symptoms when delivered by PTs than by GPs ($p = 0.02$). There was no difference between PTs and GPs in terms of physical functioning and psychological symptoms. Conclusion: Psychological interventions are effective for patients with MUS, but the effects are small and most likely of short duration. Interventions that are delivered by PTs appear to have larger effects on unexplained physical symptoms than those delivered by GPs. Whether this superiority is due to a larger number of sessions of PT interventions remains unclear from our findings.

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Does It Matter Who Provides Psychological Interventions for Medically Unexplained Symptoms? A Meta-Analysis

Heike Gerger[a, b] Michaela Hlavica[a] Jens Gaab[b] Thomas Munder[a]
Jürgen Barth[a, c]

[a]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, [b]Division of Clinical Psychology and Psychotherapy, Department of Psychology, University of Basel, Basel, and [c]Institute for Complementary and Integrative Medicine, University Hospital Zürich and University of Zürich, Zürich, Switzerland

Key Words
Medically unexplained physical symptoms · Psychological interventions · Meta-analysis · Treatment provider · Somatization · Symptom severity

Abstract
Background: Patients with medically unexplained symptoms (MUS) are difficult to treat and cause high health-care costs. Psychological interventions might be a beneficial option for treating patients with MUS, but evidence is inconsistent. This meta-analysis compares the effectiveness of psychological interventions for MUS – delivered either by psychotherapists (PTs) or by general practitioners (GPs) – with that of usual care. ***Method:*** We conducted a systematic review and meta-analysis on randomised controlled trials of psychological interventions for MUS. Physical symptoms were the primary outcome, and physical functioning and psychological symptoms were the secondary outcomes. We pooled between-group effect sizes (ESs) after the treatment and at the follow-up in random-effects meta-regressions and stratified meta-analyses. We repeated these analyses with the intervention provider, intervention dose, MUS severity and methodological quality as predictors of relative intervention effects. ***Results:*** A total of 3,225 patients in 20 studies were analysed. After the treatment, small and significant ESs were found for all 3 outcome domains (ES range: 0.13–0.19, all $p < 0.05$). Psychological interventions were more beneficial for physical symptoms when delivered by PTs than by GPs ($p = 0.02$). There was no difference between PTs and GPs in terms of physical functioning and psychological symptoms. ***Conclusion:*** Psychological interventions are effective for patients with MUS, but the effects are small and most likely of short duration. Interventions that are delivered by PTs appear to have larger effects on unexplained physical symptoms than those delivered by GPs. Whether this superiority is due to a larger number of sessions of PT interventions remains unclear from our findings.

Introduction

Patients presenting with somatic symptoms that lack a medical explanation are common in primary and secondary health-care settings, with a prevalence of 20–50% [1–4]. Such symptoms may be part of psychiatric disorders such as anxiety or depression, part of operationally defined syndromes such as chronic fatigue syndrome, irritable bowel syndrome or fibromyalgia, or simply un-

H.G. and J.B. contributed equally to this work.

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E-Mail karger@karger.com
www.karger.com/pps

Heike Gerger, PhD
Division of Clinical Psychology and Psychotherapy
Department of Psychology, University of Basel
Missionsstrasse 62, CH–4055 Basel (Switzerland)
E-Mail heike.gerger@gmail.com

specific physical symptoms for which no medical explanation could be identified [3]. The severity of these symptoms ranges from single, transient and relatively mild symptoms to multiple and/or chronic debilitating somatic complaints with poor prognosis [5, 6].

There is an important debate on the classification of these health complaints [7], the need to distinguish between medically explained and unexplained symptoms [8] and the clinical relevance of distinguishing between individual diagnostic categories [9, 10]. Accordingly, the latest revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [11] merged several of the previous categories to one diagnosis, i.e. somatic symptom disorder, which places more importance on thoughts, feelings and behaviours regarding those symptoms and, in contrast to DSM-IV, does not require symptoms to lack a medical explanation anymore. The heterogeneity of complaints that are combined within the diagnostic category of somatic symptom disorder remains high. In contrast to DSM-5, the Diagnostic Criteria for Psychosomatic Research (DCPR) [12] suggest a more fine-grain diagnostic approach with 12 psychosomatic syndromes that capture additional psychosocial variables. The debate on the classification of medically unexplained symptoms (MUS) is ongoing [13, 14].

Patients with MUS typically consult a series of physicians and medical specialists – a phenomenon often referred to as 'doctor shopping'. This behaviour does not relieve the patients' suffering but increases annual healthcare costs, which are twice as high for patients with MUS than for patients without [15, 16]. Despite the refusal of many patients to be treated by psychological means [17], psychological interventions might be a beneficial treatment option for MUS [14] and could be a promising adjunct to medical treatment [5].

Across systematic reviews and meta-analyses, psychological interventions for patients with MUS were more effective than usual care (UC) or waiting list, albeit with small effects [14, 18–22]. The most recent comprehensive meta-analysis [14] took a broad perspective with a large variety of target problems and a large number of analyses. In contrast, in this study, we aimed to address one particular research question. We narrowed down the included problems to multiple and unspecific MUS that do not relate to a medical or psychiatric disorder or syndrome and restricted our analyses to between-group analyses comparing a psychological intervention with UC in randomised controlled trials (RCTs). In particular, we looked at differential treatment effectiveness, comparing psychological interventions delivered by general practitioners (GPs) with those provided by psychotherapists (PTs). Additionally, we included the severity of MUS, the number of intervention sessions, the length of intervention sessions and the quality of the study methodology as potential moderators of relative intervention effects.

Methods

Literature Search

We searched bibliographic databases relevant to the field of psychotherapy outcome research (Embase, Medline, PsycINFO, Cochrane Controlled Trials Register and PSYNDEX) combining key words and text words that relate to psychological interventions, RCTs and MUS (online suppl. appendix A; for all online suppl. material, see www.karger.com/doi/10.1159/000380914). The initial search was conducted in December 2008. An update search was conducted in January 2013 in the PsycINFO, Medline and Cochrane Controlled Trials Register databases. We also checked the reference lists of previous systematic reviews and meta-analyses on MUS [18, 19, 23]. All records were transferred to EndNote (EndNote X3, Thomson Reuters, USA), where duplicates were eliminated and all references were screened for inclusion and exclusion criteria.

Study Selection

We included RCTs that evaluated the efficacy of a psychological intervention compared to UC in patients with multiple MUS. In particular, we included studies if they (a) analysed adult patients (at least 80% of patients included had to be older than 18 years) diagnosed with MUS (either from patient self-reports or from clinical evaluation), (b) compared at least one psychological intervention with UC, (c) assigned participants randomly to treatment conditions, and (d) were published as journal articles between January 1980 and January 2013. Psychological interventions were qualified for inclusion if they were implemented at the level of individual patients (rather than group, family or couples therapy), included face-to-face contact between the participant and the therapist (as opposed to telephone- or internet-based interaction between patient and therapist) and consisted mainly of verbal communication (as opposed to, for example, biofeedback or relaxation). We excluded studies on patients who suffered from functional somatic syndromes that focused on one particular organ system (e.g. irritable bowel syndrome) or one particular function (e.g. chronic fatigue syndrome). We also excluded studies on hypochondriasis and studies that addressed pain as the primary clinical problem (i.e. studies were excluded if more than 80% of the patient sample suffered from a pain disorder, such as low back pain). However, we included studies if hypochondriasis or pain disorders were one among other MUS. No language restrictions were imposed.

After intensive training, one researcher screened the retrieved records and excluded clearly irrelevant references. Two researchers then independently reviewed the full text of potentially relevant publications. Ambiguities were resolved by consensus with a third researcher.

Outcome Measures

The pre-specified primary outcome domain was the presence of physical symptoms (i.e. quantity, frequency or intensity). In addition, we extracted data relating to physical functioning (e.g. self-

reported functional impairment or quality of life with and without relation to physical functioning) and psychological symptoms (e.g. depression, anxiety or general psychopathology). We extracted post-treatment data (i.e. from the first assessment after the end of treatment) and follow-up data (i.e. from the last available assessment after the end of treatment). When more than one outcome measure was reported per outcome domain, we extracted the data from all reported measures. All outcome data were from self-reports (as opposed to ratings by clinicians).

Coding and Data Extraction

We assessed the profession of the intervention provider, the severity of physical symptoms as well as the type and dose of the intervention as clinically relevant characteristics of the included studies. The profession of the intervention provider was classified as either PT (mental health professionals, including PTs and psychiatrists) or GP (professionals in primary health-care service, including nurse practitioners and medical doctors). Patient samples were considered severe if all patients met the criteria of SSI 4,6 [24], suffered from somatisation disorder according to DSM-IV criteria or reported 5 MUS at minimum. Patient samples were considered non-severe if fewer MUS were present or the number of MUS was unclear. Interventions were classified into three pre-specified categories: cognitive-behavioural treatment approaches (when the psychological intervention was based on a cognitive-behavioural rationale, e.g. reattribution), other psychological interventions (e.g. disclosure intervention or psychodynamic therapy) and enhanced care (i.e. a case manager or health educator assisted the GP). We then assessed the number of sessions as well as the length of sessions as indicators of the intervention dose.

We considered the concealment of treatment allocation [25, 26] and the adequacy of analyses [27] as indicators of the methodological quality of the included studies. The concealment of allocation was considered adequate if the investigators responsible for patient selection could not foresee which treatment would be next before allocating patients to treatments. Analyses were considered adequate if all recruited patients were analysed in the group to which they were originally allocated, regardless of the intervention they had received (ITT principle). Analyses were considered inadequate if effect sizes (EFs) could not be calculated on the total randomised sample.

All data were extracted in duplicate on a standardised and computerised form in Epidata 3.1 (The Epidata Association, Denmark) by 2 independent investigators (M.H. and a MSc student). Both investigators were trained in a 2-day workshop with a manual that included operational descriptions of all relevant data. Disagreements were resolved by consensus.

Data Analysis

Standardised mean differences (d) were calculated with small sample corrections, as recommended by Hedges and Olkin [28]. ESs of 0.20, 0.50 and 0.80 were considered as small, moderate, and large, respectively [29]. If standard deviations were not provided, ESs were computed by transforming other statistics (e.g. standard errors, confidence intervals or other indicators). We used the formulas provided by Lipsey and Wilson [30]. ESs were calculated for post-treatment and follow-up data for each outcome domain. In cases where multiple measures were reported per outcome domain, we averaged the ESs and calculated the standard errors using the mean number of patients across measures. Results from ITT analyses were preferred to analyses based on treatment completers only, because ITT analyses have been shown to provide more conservative results compared to completer analyses [31].

We applied standard inverse variance-weighted random-effects meta-analyses in order to quantify the overall intervention effect and the overall heterogeneity between primary studies. p values for interaction effects were derived from random-effects meta-regressions using a residual maximum likelihood to estimate the additive (between-study) component of variance τ^2. Standard errors were calculated using the method developed by Knapp and Hartung [32] and were tested for statistical significance (two-tailed) with the t distribution. Using this procedure in meta-regression reduces false-positive rates compared to z tests [33].

We first conducted meta-analyses without including any predictor for each type of outcome domain and for post-treatment and follow-up data. We then performed outlier analyses by drawing Galbraith plots. We excluded studies from further analyses if (a) they were clearly identified as outliers by the outlier analysis and (b) if the confidence intervals of the respective study did not overlap with the confidence interval of the overall effect estimate.

We then included the potential moderators as single predictors in meta-regression analyses and conducted stratified meta-analyses. In case of more than one significant moderator per outcome domain, we checked for potential interaction effects between the significant moderators by performing multiple meta-regressions, including significant study characteristics as predictors as well as an interaction term (according to Shadish and Sweeney [34]). In addition, we checked for colinearity among significant predictors by examining pairwise correlations.

Heterogeneity of the ES within each outcome domain between the studies was assessed by τ^2 [35, 36]. Higher τ^2 values indicate greater variability between studies than would be expected due to chance alone. Based on our definition of small, moderate and large differences between interventions, we classified τ^2 as follows: $\tau^2 = (0.2/2)^2 = 0.01$ was considered to represent low heterogeneity, $\tau^2 = 0.0625$ $[(0.5/2)^2]$ moderate heterogeneity and $\tau^2 = 0.16$ $[(0.8/2)^2]$ high heterogeneity between studies. τ^2 has been shown to be independent of the number of studies and the number of patients included in the meta-analysis (i.e. no increase with large numbers of studies or large sample sizes) [35, 36].

Meta-analyses and meta-regressions were performed with the software package STATA 11.2 using the commands 'metan' and 'metareg' [37]. We explored the presence of the small sample bias by assessing funnel plot asymmetry with a regression test [38], which was performed with the 'metabias' procedure.

Results

Twenty studies met the inclusion criteria for the present meta-analysis [39–58]. We identified 850 records through database searching and screening of reference lists of previous systematic reviews and meta-analyses. We screened 675 records by title and abstract after duplicates had been removed. Of the 114 full-text articles that were assessed for eligibility, 6 were excluded as they were multiple publications of one and the same study, and a

further 88 were excluded because the population, the intervention, the study type or the study design did not match the inclusion criteria (see online suppl. appendix B for the flow chart of study selection).

Study Characteristics

A total of 3,225 patients were randomised to interventions, with a median of 117 patients per study (range: 10–911). The characteristics of the included studies are summarised in online supplementary appendix C. One study was published in 1995, whereas all other studies were published between 2000 and 2010. Thirteen studies were carried out in Europe, 4 in the US, 2 in Sri Lanka, and 1 study was carried out in Australia. Physical symptoms were assessed in 14 studies, physical functioning in 15 and psychological symptoms also in 15. Follow-up assessments were available in 11 studies. Time points of follow-up assessments varied between 6 and 24 months after beginning the intervention.

In 11 studies, at least some patients reported comorbid mental disorders. In 9 studies, some of the patients faced a difficult living situation (e.g. unemployment). However, only in a minority of the samples (6 of 21 studies) did more than 80% of the patients report additional problems (i.e. mental disorder or living situation; see online suppl. appendix C). Nine studies were classified as including patients with severe MUS, whereas 11 studies were classified as including patient samples with non-severe MUS.

Patients were treated by GPs in 13 studies and by PTs in 7 studies. Psychological interventions were based on CBT approaches in 11 studies, on other psychological interventions in 5 studies and on enhanced care in 4 studies. In all studies, UC was used as a control group. The median number of sessions per study was 6 (range: 2–15), and the reported mean length of a session of psychological interventions was 41 min (range: 13–70). Studies varied across intervention providers with regard to the number of sessions (median of 9 for PTs and median of 5 for GPs) and the length of sessions (mean of 49 min for PTs and mean of 33 min for GPs). The correlation between the number of sessions and the treatment provider was small to moderate ($r = 0.34$, $p = 0.23$), and the correlation between the session length and the treatment provider was moderate ($r = 0.48$, $p = 0.08$).

In terms of methodological quality, 13 studies reported data from ITT analyses and 7 studies reported adequate strategies for concealment of allocation of patients to interventions. Only 4 studies fulfilled both criteria of higher quality.

Overall Effectiveness

At the end of the intervention, the relative effect between psychological interventions and UC was small for physical symptoms ($d = 0.22$; $k = 14$; 95% CI 0.04, 0.40; $p = 0.02$), physical functioning ($d = 0.19$; $k = 15$; 95% CI 0.02, 0.36; $p = 0.03$) and psychological symptoms ($d = 0.13$; $k = 15$; 95% CI –0.00, 0.27; $p = 0.05$). Heterogeneity was moderate to low ($\tau^2 = 0.07$ for physical symptoms and physical functioning, and $\tau^2 = 0.03$ for psychological symptoms). For physical symptoms, 1 study was identified as an outlier (i.e. van der Feltz-Cornelis et al. [58] for physical symptoms; see online suppl. appendix D). The removal of the outlier slightly reduced the relative effect as well as the heterogeneity for physical symptoms ($d = 0.15$; $k = 13$; 95% CI 0.00, 0.30; $\tau^2 = 0.03$). The effect remained statistically significant ($p = 0.048$).

At the follow-up, the relative effect between psychological interventions and UC was small but not statistically significant ($d = 0.21$; $k = 11$; 95% CI –0.02, 0.44; $p = 0.08$ for physical symptoms; $d = 0.13$; $k = 10$; 95% CI –0.04, 0.30; $p = 0.13$ for physical functioning; and $d = –0.05$; $k = 9$; 95% CI –0.18, 0.08; $p = 0.47$ for psychological symptoms). Heterogeneity was moderate to high for physical symptoms ($\tau^2 = 0.11$), low to moderate for physical functioning ($\tau^2 = 0.04$) and low for psychological symptoms ($\tau^2 = 0.01$). The study of van der Feltz-Cornelis et al. [58] was again identified as an outlier for physical symptoms and physical functioning. Excluding this outlier reduced the relative effect between psychological interventions and UC ($d = 0.08$; $k = 10$; 95% CI –0.05, 0.21 for physical symptoms; and $d = 0.05$; $k = 9$; 95% CI –0.07, 0.17 for physical functioning). Neither effect was statistically significant (all $p > 0.20$). Heterogeneity was low with $\tau^2 = 0.01$ for all three outcome domains.

Some funnel plots suggested asymmetry, indicating that smaller studies showed larger effects of psychological interventions compared with UC. However, the corresponding regression test was significant for psychological symptoms after the treatment only ($p = 0.01$; all other $p > 0.12$). Heterogeneity was considerably reduced after excluding the outlier. Therefore, we excluded the study by van der Feltz-Cornelis et al. [58] from the moderator analyses of physical symptoms after the treatment and at follow-up as well as from moderator analyses of physical functioning at follow-up.

Moderator Analyses

Table 1 shows the results from meta-regressions, including the methodological and clinical characteristics as single predictors. For physical symptoms, significant

Table 1. Results from meta-regressions after the treatment including clinical and methodological study characteristics as moderators of relative effects between psychological interventions and UC

Outcome dimension	After treatment					At follow-up				
	k	B	95% CI	τ^2	p	k	B	95% CI	τ^2	p
Physical symptoms										
Provider	13	0.32	0.07, 0.57	0.00	**0.02**	10	0.29	0.04, 0.53	0.00	**0.03**
Severity	13	0.02	−0.41, 0.45	0.04	0.93	10	0.07	−0.37, 0.51	0.02	0.73
Number of sessions[a]	11	0.06	0.01, 0.11	0.00	**0.03**	9	0.05	0.01, 0.10	0.00	**0.03**
Session length[b]	11	−0.06	−0.92, 0.81	0.05	0.88	9	0.19	−0.62, 1.00	0.03	0.60
Concealment	13	−0.05	−0.43, 0.33	0.04	0.79	10	−0.09	−0.44, 0.27	0.01	0.59
ITT	13	0.12	−0.27, 0.51	0.04	0.52	10	0.12	−0.21, 0.45	0.01	0.42
Physical functioning										
Provider	15	−0.05	−0.48, 0.38	0.07	0.80	9	0.19	−0.13, 0.50	0.01	0.20
Severity	15	−0.19	−0.55, 0.17	0.06	0.27	9	−0.11	−0.45, 0.22	0.01	0.45
Number of sessions[a]	10	0.04	−0.03, 0.10	0.03	0.27	7	0.04	−0.02, 0.09	0.00	0.16
Session length[b]	9	−0.06	−0.77, 0.64	0.04	0.84	7	−0.40	−1.12, 0.32	0.00	0.21
Concealment	15	−0.11	−0.49, 0.27	0.07	0.54	9	−0.11	−0.45, 0.23	0.01	0.46
ITT	15	−0.06	−0.44, 0.33	0.07	0.76	9	0.18	−0.09, 0.46	0.01	0.16
Psychological symptoms										
Provider	15	0.11	−0.22, 0.44	0.02	0.48	9	0.11	−0.24, 0.45	0.01	0.50
Severity	15	−0.14	−0.43, 0.16	0.02	0.33	9	0.06	−0.36, 0.48	0.02	0.74
Number of sessions[a]	12	0.01	−0.03, 0.05	0.02	0.47	8	0.01	−0.05, 0.08	0.03	0.60
Session length[b]	12	0.02	−0.45, 0.49	0.00	0.93	8	0.48	−0.16, 1.12	0.00	0.12
Concealment	15	−0.03	−0.34, 0.27	0.03	0.82	9	0.10	−0.28, 0.47	0.02	0.56
ITT	15	−0.07	−0.40, 0.26	0.03	0.66	9	−0.05	−0.44, 0.33	0.02	0.75

B = Regression coefficient from meta-regression; k = number of included study ESs; τ^2 = variability between studies. Significant p values are printed in bold.

[a] Continuous variable (range: 2–15 sessions). [b] Continuous variable (range: 0.22–1.17 h).

moderating effects were found for the provider of the intervention (p = 0.02) and for the number of sessions (p = 0.03). Superiority of psychological interventions over UC was larger in studies in which PTs delivered the intervention (fig. 1) and in studies with a higher number of sessions. None of the other predictors included had a significant moderating effect on the relative intervention effect for our secondary outcomes, namely, physical functioning or psychological symptoms (all p > 0.27). At follow-up, the results obtained after the treatment were confirmed: the provider of the intervention and the number of sessions were the only significant moderators (p = 0.03 in both cases) for the primary outcome, and there were no significant moderators for the secondary outcomes.

Additional Exploratory Analyses

We restricted the following exploratory analyses to the primary outcome (i.e. physical symptoms) for which the intervention provider and the session number were significant moderators. First, we tested for a possible interaction between the intervention provider and the intervention dose. Table 2 presents the results from meta-regressions that investigated whether the association of the number of sessions with outcome was the same for GPs and PTs. Therefore, the analyses were stratified for the intervention provider and included the number of sessions as covariate. When testing for the interaction in a multiple meta-regression, neither the two predictors nor the interaction term was statistically significant (all p > 0.39 after the treatment and all p > 0.54 at follow-up).

In a final exploratory analysis, we checked for an interaction between the intervention provider and MUS severity, although severity was not a significant moderator of the intervention effect. Table 2 presents the results from meta-regressions that investigated whether the superiority of PTs over GPs depended on symptom severity. Therefore, the analyses were stratified according to MUS severity at the beginning of the psychological interven-

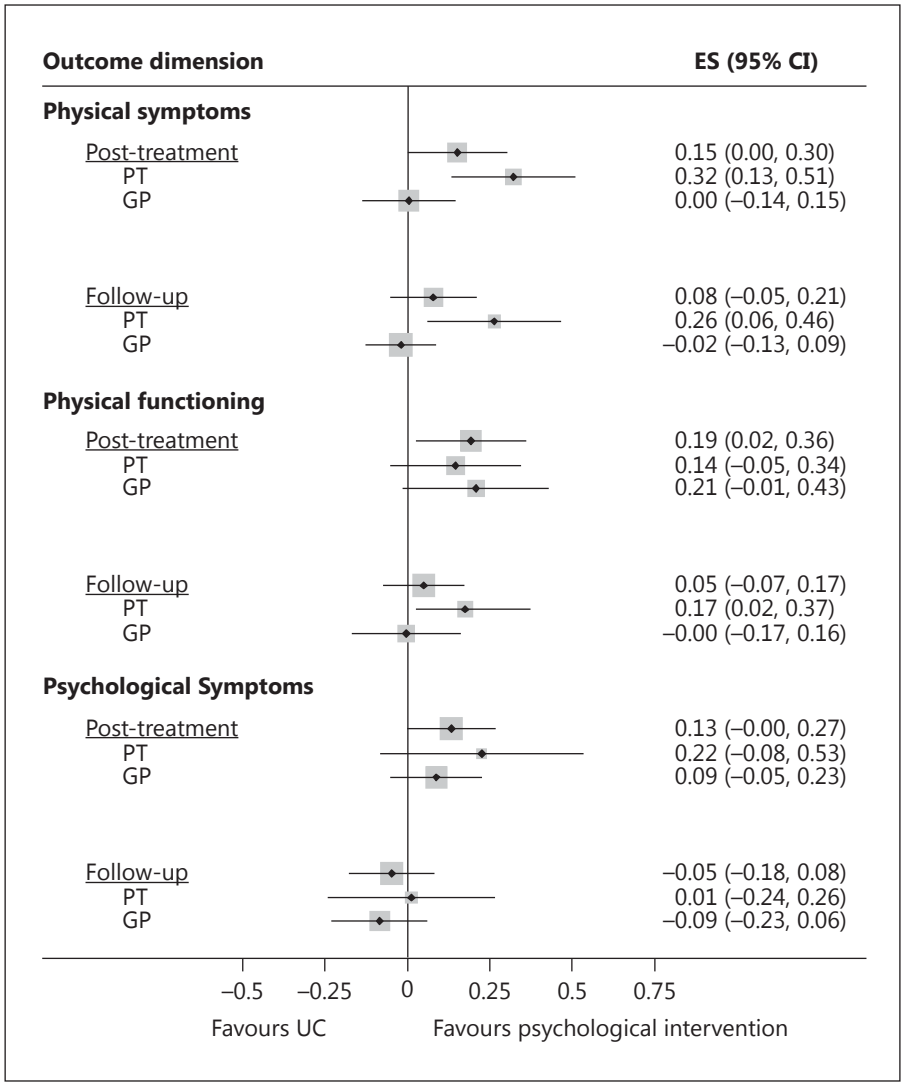

Fig. 1. Relative effects between psychological interventions and UC (overall and stratified according to the intervention provider, i.e. GP vs. PT). Positive ESs indicate superiority of the psychological intervention.

Table 2. Results from stratified meta-regressions to detect possible interactions between predictors of relative effects and psychological interventions and UC for physical symptoms

Predictor	After treatment					At follow-up				
	k	B	95% CI	τ^2	p	k	B	95% CI	τ^2	p
Number of sessions										
GP[a]	5	0.10	–0.17, 0.37	0.03	0.33	4	–0.01	–0.34, 0.32	0.00	0.94
PT[b]	6	0.03	–0.09, 0.15	0.01	0.48	5	0.05	–0.08, 0.17	0.00	0.31
Provider										
Non-severe	5	0.15	–1.40, 1.69	0.18	0.78	3	0.51	–5.28, 6.29	0.08	0.47
Severe	8	0.34	0.06, 0.62	0.00	**0.02**	7	0.30	–0.01, 0.61	0.00	0.06

B = Regression coefficient from meta-regression; k = number of included study ESs; τ^2 = variability between studies within one stratum. Significant p values are printed in bold.

[a] Range of the continuous covariate 'number of sessions' in the GP stratum: 2–15. [b] Range of the continuous covariate 'number of sessions' in the PT stratum: 4–12.

tion and included the intervention provider as covariate. PTs had larger effects (d = 0.35; 95% CI 0.14, 0.55; τ^2 = 0.00; k = 4) than GPs in studies with severe MUS (d = 0.01; 95% CI –0.10, 0.12; τ^2 = 0.00; k = 4; p for interaction = 0.02) but not in studies with non-severe MUS (p for interaction = 0.78). When we entered severity and provider in addition to an interaction term in a multiple meta-regression, however, neither predictor remained statistically significant (all p > 0.69). At follow-up, the results found after the intervention were confirmed, with PTs showing larger effects than GPs only in studies with severe MUS samples. Psychological interventions were significantly more effective than UC when provided by PTs in samples with severe MUS (d = 0.29; 95% CI 0.06, 0.53; τ^2 = 0.01; k = 3), but there was no difference between psychological interventions and UC when psychological interventions were provided by GPs (d = –0.01; 95% CI –0.11, 0.10; τ^2 = 0.00; k = 4). This difference in relative intervention effects between PTs and GPs in the severe MUS samples was only borderline significant (p for interaction = 0.06). In contrast, no difference was found between GPs and PTs in the studies with non-severe samples (p for interaction = 0.47). In the multiple meta-regression based on the follow-up data, again, neither predictor was statistically significant (all p > 0.27).

Discussion

Psychological interventions were more effective than UC for physical symptoms, physical functioning and psychological symptoms after treatment termination (fig. 1). The superiority of psychological interventions over UC in reducing physical symptoms was more pronounced when the intervention was delivered by PTs than by GPs. This pattern appears in most of the conducted analyses (fig. 1). However, only for physical symptoms assessed after the treatment was the pattern statistically significant. An exploratory analysis revealed that PT interventions were superior to GP interventions, particularly for patients with severe MUS. In contrast, similar intervention effects were found for patients with non-severe MUS when psychological interventions were delivered either by PTs or GPs. However, as the number of sessions was also associated with relative intervention effects, it is possible that the impact of the intervention provider on the outcome is confounded with a dose effect (see below). Interestingly, the session length was not associated with intervention effects. We found no robust evidence for long-term intervention effects. Besides the outlier, only 2 out of 11 studies showed a significant long-term effect of psychological interventions on physical symptoms, and no study showed significant long-term effects on physical functioning or psychological symptoms (see online suppl. appendix E).

Our results confirm the general conclusion of recent meta-analyses [14, 18] that psychological interventions are effective treatments for MUS, albeit with small ESs. Small between-group ESs may be explained by a large amount of improvement of MUS in UC or even without treatment [6, 59]. The somewhat smaller ES in our meta-analysis compared with the previous ones may be explained by our restriction to RCTs when compared with Kleinstäuber et al. [18] and by excluding waiting list as comparator when compared with van Dessel et al. [14]. The particularly low ES for physical functioning and psychological symptoms may be a consequence of inadequate assessment. In future studies, the use of assessment tools that are based on the DCPR, which has been shown to be highly sensitive in identifying psychological distress and characterizing patients' psychological response to medical illness [60, 61], might reveal larger effects particularly on psychosocial variables as outcome. Our results suggest that patients with severe MUS should be treated by PTs, which is in line with a recent trial [62]. In contrast, patients with non-severe MUS may be treated by either PTs or GPs. The need for more elaborated treatments for patients with severe MUS is also reflected by the previous finding that those patients with MUS who have a larger number of symptoms at baseline show less improvement in UC or without treatment [6].

Several aspects need attention when trying to explain the superiority of PT-delivered interventions over GP interventions. On the one hand, when compared to GPs, PTs might offer additional explanations for MUS and thus contribute to increasing the patients' ability to tolerate symptoms [63]. On the other hand, patients seeking support from GPs may differ in their motivation from those who seek support from PTs [64, 65]. Those patients who seek treatment by a PT may, for instance, be more motivated to change, or may be more open to changing their illness perception, which in turn might influence a patient's experience and behaviour [66]. Finally, the superiority of PTs might be due to a dose difference between PT and GP psychological interventions: in particular, patients with higher symptom severity may benefit from a higher intervention dose. In our analyses, the number of sessions was indeed higher in studies with PTs than in studies with GPs. When trying to disentangle the effects of the two potential moderators (dose and provider), we found no evi-

dence of a strong collinearity, neither did we find evidence of an interaction effect of both variables on the outcome. However, the multiple meta-regressions may have lacked the power to reveal statistically significant interaction effects. Thus, our results document the superiority of PT interventions over GP interventions without offering an explanation. Further studies should address the outlined issues by directly comparing psychological interventions that are delivered by PTs versus those delivered by GPs. In addition, explorations of the possible mechanisms that underlie the superiority of PTs over GPs may include manipulating the number of sessions, controlling patients' self-selection of PTs or GPs, and controlling the rationale that therapists offer their patients as explanation for their symptoms. The interesting finding that only the number of sessions, but not the session length is associated with intervention effects needs further attention.

Some limitations need to be considered when interpreting the results presented. First, we excluded studies on somatoform pain disorder. It has been previously shown that, particularly in studies on pain, the question of whether the symptoms indeed lack a symptomatic pathology remains unclear [67]. We therefore excluded studies that primarily addressed pain and came up with a pool of included studies with only small to moderate between-study heterogeneity of ES estimates. Before generalizing our results to patient populations that were not included in our meta-analysis, the results presented here need to be replicated in the respective patient populations. Second, we refrained from analysing additional potential moderators in order to minimise the number of false-positive results due to multiple testing. We restricted the number of moderators to variables that were adequately reported in the included studies or known to be relevant predictors of the effectiveness of psychological interventions for MUS. We cannot rule out the possibility that additional moderators may have affected intervention effects. However, heterogeneity statistics indicated low between-study heterogeneity in the final analyses and thus imply no need to explore additional potential moderators. Third, we did not pool data regarding healthcare utilisation and dropout rates. Indicators of healthcare utilisation vary largely across individual studies (e.g. assessment of visits to GPs and specialists, costs of medication or number of hospitalisation days), and the reporting of dropout rates mostly does not allow distinguishing between patients who refused to complete the intervention and those who refused only the outcome assessment. Thus, the validity of both outcome domains remains unclear. Fourth, the results based on differentiating between studies on severe versus non-severe MUS should be regarded as preliminary. The distinction between severe and non-severe patient samples was done on an exploratory basis and did not take into account results from subgroup analyses in primary studies, such as for example the one reported by Toft et al. [57]. Further confirmation of the observed patterns is absolutely essential. Finally, the number of included studies was somewhat small due to our rather strict inclusion criteria in order to get a homogeneous pool of studies with similar complaints. The results from our stratified analyses therefore lack precision in many cases and need to be confirmed in primary studies that are designed and adequately sized in order to test the respective research questions. In order to use as much data as possible, we approximated the ES estimate in one case in which the authors reported that 'The general pattern was the same at six and 12 month follow ups (data not shown)' [50, p. 4]. In this case, we used the same data for the calculation after the treatment and at follow-up. Excluding the approximated data in the respective sensitivity analyses led to a slightly reduced precision but did not change the findings.

From a clinical perspective, our results suggest that patients with MUS who did not respond to UC should be treated with psychological interventions, although all intervention effects were small. For those patients who have suffered from their symptoms for a long time and are described as treatment resistant, even small and short-term intervention effects, indicating some symptom change over even a short period of time, can be regarded as clinically relevant. Short-term improvement could serve as a first step that may contribute to reappraisals of the MUS and eventually stimulate changes in health behaviour [66, 68]. In this sense, psychological interventions in particular may contribute to challenging the perception of many MUS patients that change is impossible [69]. There is, however, potential for improvement in the treatment of patients with MUS. Complex treatment packages including psychological as well as technologically driven interventions, which focus on psychophysiology, have recently shown promising results [70]. Whether such complex treatment regimen for MUS may lead to better or more long-lasting improvement should be addressed further in well-designed primary studies.

To conclude, this meta-analysis shows that psychological interventions are promising for patients with MUS. The psychological interventions of PTs are more effective in treating unexplained physical symptoms than those delivered by GPs. The collaboration between GPs and PTs may be important for the successful treatment of

MUS and particularly for treating patients with severe MUS. Such collaborative interventions have been shown to be superior compared to enhanced care of GPs alone [71]. Our analyses pointed out several research questions, including the apparent differential need for the treatment of patients with severe versus non-severe MUS, which remain inadequately answered to date.

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